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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/817,312	04/01/2004	Stephen S. Palmer	05558.0011.NPUS04	1876

7590 05/06/2005

Attention: IP Prosecution
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EXAMINER	
DESAI, ANAND U	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 05/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/817,312	PALMER ET AL.	
	Examiner	Art Unit	
	Anand U. Desai, Ph.D.	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32,34-48 and 50-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32,34-48 and 50-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1-32, 34-48, and 50-72, drawn to a method for stimulating ovarian follicular growth in a female comprising administering to a female a medicament comprising a phosphodiesterase inhibitor in the reply filed on January 11, 2005 is acknowledged. Applicants elect phosphodiesterase 4 inhibitors as the species for search purposes. Claims 33, 49, and 73-78 are cancelled.

The requirement is still deemed proper and is therefore made FINAL.

Priority

2. This application claims priority to U.S. Provisional application 60/458,955 filed April 1, 2003.

Information Disclosure Statement

3. The information disclosure statements (IDSs) submitted on August 6, 2004 and January 31, 2005 are being considered by the examiner. There are duplicate 1449 forms filed on August 5, and 6 of 2004. The August 6, 2004 forms have an Office of Initial Patent Examination date stamp on all 13 pages and are therefore being signed.

Specification

4. The disclosure is objected to because of the following informalities:

5. The brief description of the drawings section does not identify which cells are being described in the respective figures 10A, 10B, and 10C. Suggest placing ",10A)" next to "ovarian dispersate", and ", 10B,10C)" next to "JC410/FSHR."

6. On page 1, line 21, the comma before the abbreviation "(FSH)" does not appear to be required.

7. On page 7, line 184, the beginning of paragraph 17 is missing a capital letter or the word, "In."

8. The use of the trademark "ARIFLO" has been noted in this application. For example on page 11, line 284, and page 26, line 725. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

9. On page 53, line 1468, paragraph 138, there appears to be a typographical error when describing the time?

10. On page 62, paragraph 160, the 2nd sentence is unclear. Is it meant to read "Low concentrations of Piclamilast **were** ~~was~~ not sufficient to induce...?"

Appropriate correction is required.

Claim Objections

11. Claim 4 is objected to because of the following informalities: The abbreviation FSH should be spelled out as follicle stimulating hormone at the first occurrence.

12. In claim 10, the abbreviation hCG should be spelled out as human chorionic gonadotrophin at the first occurrence.

13. In claims 14, and 15, the standard Markush language is preferred. Suggest, "...at least one PDE type selected from the group consisting of ~~from~~ PDE 1, PDE 5, and PDE 6."

Appropriate correction is required.

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 1-7, 14-32, 34, 35, 37-39, 41-47, 50, 51, 54-56, 63, 64, 67, and 69 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-30 of copending Application No. 10/498,639. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application are drawn to a method of follicular development and ovulation induction in a female host comprising the administration of an agent which increases follicle stimulating hormone concentration and administering a non-polypeptide cAMP level modulator that includes an inhibitor of a phosphodiesterase 4 isoform. The current claims are drawn to a method of stimulating ovarian follicular growth in a female comprising administering a medicament comprising a phosphodiesterase 4 inhibitor, and follicle stimulating hormone, or

an agent having follicle stimulating hormone activity. Therefore, the compositions/medicament is structurally the same and would be expected to produce the same functional effect.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. Claims 1, 2, 3, 32, 34, and 35 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2, 3, and 28 of copending Application No. 10/014,812. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application are drawn to a method of inducing ovulation in a female host comprising administering an inhibitor of phosphodiesterase type 4. The current application claims are drawn to a method of stimulating ovarian follicular growth or follicle maturation in a female comprising administering a medicament comprising a phosphodiesterase 4 inhibitor. Therefore, the compositions/medicament is structurally the same and would be expected to produce the same functional effect.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

17. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

18. Claims 10, 11, and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

19. The term "sufficient" in claims 10, and 11 is a relative term, which renders the claims indefinite. The term "follicular growth" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

20. Claim 35 is claiming a trademarked product, "ARIFLO." If the trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of the 35 U.S.C. 112, second paragraph. *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. In fact, the value of a trademark would be lost to the extent that it became descriptive of a product, rather than used as an identification of a source or origin of a product. Thus, the use of a trademark or trade name in a claim to identify or describe a material or product would not only render a claim indefinite, but would also constitute an improper use of the trademark or trade name.

Claim Rejections - 35 USC § 102

21. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

22. Claims 1-7, 14-32, 34, 35, 37-42, 44-47, 50, 51, 54, 55-58, 62, and 63 are rejected under 35 U.S.C. 102(e) as being anticipated by Palmer, S. et al. (U.S. Patent Publication US2002/0065324 A1; 102(e) date is August 11, 2000).

Palmer, S. et al. disclose methods of improving fertility in a female host comprising the administration of a non-polypeptide cyclic adenosinemonophosphate (cAMP) level modulator to the female host. The preferred non-polypeptide cAMP level modulators include phosphodiesterase inhibitors, particularly inhibitors of phosphodiesterase 4 isoforms (see paragraph 11). Palmer, S. et al. describe the effects of a PDE inhibitor on ovulation, in the presence of a subeffective dose of hCG in vivo. Mature ovarian follicles generated in immature female rats by treatment with an effective dose of FSH (2.16 IU/rat/injection; bidx2 days; embodiments of FSH are described in paragraph 43) were induced to ovulate with a single injection of hCG. hCG was administered at a sub-effective dose (3 IU) with and without a single injection of a PDE inhibitor (50, 10, and 1 mg/kg) at the time of the final FSH injection. The results demonstrate that a PDE inhibitor enhances hCG-stimulated ovulation (see Example 3). Palmer, S. et al. disclose the stimulation of follicular development prior to the administration of a non-polypeptide cAMP level modulator, which comprises the administration of an agent, which

increases FSH concentrations during the follicular phase of the host's ovulatory cycle (see paragraphs 13, 42, 43, 45, 66 and claims 7-21, current application, claims 1-7, 14-32, 34, 35, 37-42, 44-47, 50, 51, 54, 55-58, 62, and 63).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claim Rejections - 35 USC § 103

23. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

24. Claims 1-11, 14-32, 34, 35, 37-47, 50-59, and 62-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Palmer, S. et al. (U.S. Patent Publication US2002/0065324 A1; 102(e) date is August 11, 2000) in view of Bowman, W.C et al. (Textbook of Pharmacology, 2nd edition pages 20.20-20.21 (1980)).

The teachings of Palmer, S. et al. are disclosed above in the 102(e) rejection. Palmer, S. et al. does not disclose, which time in the menstrual cycle the compounds should be administered. Bowman, W.C. et al. describes the temporal pattern and concentration of

hormonal changes associated with the menstrual cycle (see Figure 20.17). Bowman, W.C. et al. states toward the end of the proliferative phase, as the follicle matures just prior to ovulation, there is a sharp rise in release of oestradiol (see page 20.21, 1st column, 5th paragraph).

Therefore, a person having ordinary skill in the art would have been motivated to administer the PDE inhibitor, and the cycling hormones prior to ovulation, to mimic the follicle growth during the menstrual cycle, which leads to the subsequent oocyte ovulation. Thus, it would have been obvious to the person having ordinary skill in the art to administer the PDE inhibitor as disclosed by Palmer, S. et al. and the cycling hormones at the time and concentration being described by Bowman, W.C. to stimulate ovarian follicle growth and maturation in a female (current application, claims 1-11, 14-32, 34, 35, 37-47, 50-59, and 62-65).

25. Claims 66-72 rejected under 35 U.S.C. 103(a) as being unpatentable over Palmer, S. et al. (U.S. Patent Publication US2002/0065324 A1; 102(e) date is August 11, 2000) as applied to claims 1-11, 14-32, 34, 35, 37-47, 50-59, and 62-65 above, and further in view of Barbieri, R. et al. (Endocrine Reviews 20(3): 249-252 (1999)).

The teachings of Palmer, S. et al. are disclosed above in the 102(e) rejection. Palmer, S. et al. does not disclose the suppression of endogenous FSH and LH by the administration of GnRH or an analog thereof to a female. Barbieri, R. et al. discloses the improvement in ovarian stimulation with exogenous gonadotropins and pituitary suppression with gonadotropin-releasing hormone analogues. Barbieri, R. et al. disclose suppression of pituitary gonadotropin secretion with a GnRH analogue permits longer ovarian stimulation, which results in the development of a greater number of large mature follicles. This permits the retrieval of a greater number of

competent oocytes, which increases the number of healthy embryos created and thereby improves the pregnancy rate in in-vitro fertilization (see page 250, section III. Pituitary Suppression Improves IVF-ET Success: GnRH Agonist Analogues, particularly last paragraph, 2nd column, and Figure 1).

Therefore, a person having ordinary skill in the art would have been motivated to administer the GnRH analogue, because of the improved pregnancy rate due to greater number of larger mature follicles. Thus, it would have been obvious to the person having ordinary skill in the art to administer the GnRH analogue as described by Barbieri, R. et al. prior to the administration of the PDE inhibitor and the FSH hormone as disclosed by Palmer, S. et al. to stimulate ovarian follicle growth, and thus retrieve a greater number of competent oocytes to harvest and use in in-vitro fertilization for a female (current application, claims 66-72).

Art of Record

The reason of allowance of co-pending application 10/014,812, which describes the state of the art: U.S. Patent 6,423,710 contains the motivation of using the PDE4 inhibitor for induction of ovulation, which is based on elevation of cAMP level by the inhibitor, within granulose cells; 6,423,710 does not fairly teach or suggest inducing in vivo ovulation in a female host by administering to the host the PDE4 inhibitor. Additionally, applicants point out that assumption made by the Tsafriri that suppression of cAMP-specific PDE may enhance the gonadotropin induction of ovulation is only limited to in vitro studies. Applicants stress that Tsafriri does not teach in vivo application of the PDE inhibitory compound(s) to induce ovulation. (2) Before this invention, the field of PDE4 inhibitor confronts unpredictability,

especially as to its roles in reproductive biology, e.g., Jin et al. reference has indicated that the PDE4 knockout exhibits an impaired ovulation (Proc. Natl. Acad. Sci. (1999) 96, 1 1998-12003, see Results, section Effects of the Disrupted PDE4D Gene on Female Fertility, and Figure 5A); and, on page 1324, Conti's Minireview reference (Mol. Endocrinol. (2000) 14, 1317-1327) has discussed that use of PDE indictors in endocrine cell responses (note that ovulation is one of such the responses) is an unexplored field. Therefore, the obviousness rejection based on 6,423,710 lacks a reasonable expectation of success, which is the standard with which obviousness is determined.

Conti, M. et al. (U.S. Patent 6,110,471) claim a contraceptive device for use in preventing oocyte maturation in a female mammal, comprising a PDE3-specific inhibitor (see Claim 14).

Manabe, N. et al. (Journal of Reproduction and Development, Vol. 50, No. 5, 493-514 (2004)) have investigated the molecular mechanism of selective follicular atresia in mammalian ovaries, and have reported that follicular selection dominantly depends on granulosa cell apoptosis (see Entire document).

Brinton, L. et al. describes the use of ovulation-inducing agents being linked with an increase incidence of various cancers (see Brinton, L. et al. Fertility and Sterility, Vol. 83, No. 2, 261-274 (2005), see Entire document, particularly Background section).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anand U. Desai, Ph.D. whose telephone number is (571) 272-0947. The examiner can normally be reached on Monday - Friday 7:00 a.m. - 3:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on (517) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

April 26, 2005

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER